Atty. Dkt. No. 034258-1401

REMARKS

Claims 32-46 are pending in this application. Claims 32, 35 and 41-44 have been amended to further define the invention. The amendments and new claims find support in the application and originally filed claims. For example, support for the implant materials clause in claims 42 and 44 can be found at p. 4, lines 12-22. Accordingly, the present amendments raise no issue of new matter.

Rejection under 35 U.S.C. § 112 – Written Description

The rejection of claims 39 and 40 as allegedly lacking written description is respectfully traversed. The Examiner asserts that the specification fails to describe any spacer molecules (including agarose) which function to reduce nonspecific binding. Office Action, page 2, lines 22-24. Applicant respectfully disagrees. The specification discusses use of an adsorption preventing layer to prevent nonspecific adsorption and describes agarose as an example of a spacer molecule.

> In order to **exclude the nonspecific adsorption** of the mediator molecules, which can be up to 30% of the adsorbed mediator molecules on the metal surface, it is further preferred in the scope of the present invention to first couple an **adsorption-preventing layer of spacer molecules such as for example agarose** to the surface of the implant on which the metal oxide layer is provided, to which adsorption-preventing layer the mediator molecules can then be coupled. A prevention of nonspecific adsorption can make sense in order to for example preclude a blocking of BMP-receptors as a result of conformational changes of the BMP-proteins following nonspecific adsorption to the surface. The invention is therefore also directed to such a method for the formation of a **nonspecific binding-preventing coating** on the metal oxide layer and subsequent coupling of the mediator molecules. The use of a coating of agarose for this purpose is preferred.

Specification p. 8, line 35 to p. 9, line 14. Thus the specification clearly describes spacer molecules that would act as nonspecific binding agents. The specification also clearly refers to agarose as a preferred spacer molecule. In addition, Example 12 shows how agarose can be used as a spacer molecule.

In view of the above, Applicant respectfully submits that there is ample written

description support in the specification for claims 39 and 40. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112 - Indefiniteness

Claims 35-37: The rejection of claims 35-37 as allegedly indefinite for use of the term "bone growth factor" is respectfully traversed. Contrary to the Examiner's assertion, one of ordinary skill would understand and readily determine the scope of the term "bone growth factor" as used in the claims in view of the specification. However, in order to expedite prosecution, the disputed term has been removed from claims 35-37. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claims 41-44: The rejection of claim 41-44 as allegedly being indefinite because the claims refer to methods of immobilizing a mediator molecule on an implant material rather than producing an implant material is respectfully traversed. Contrary to the Examiner's assertion, claims 41-44 clearly indicate the creation of an implant rather than the production of implant material. One of ordinary skill would understand and readily determine the scope of the implants of claims 41-44 as used in the claims in view of the specification. However, in order to expedite prosecution, reference to modification of an implant has been added to claims 41-44 as suggested by the Examiner. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 42: The rejection of claim 42 as allegedly being indefinite for using one Markush group to further define another Markush group in claim 32 is acknowledged. The Markush group has been eliminated from claim 42. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Rejection under 35 U.S.C. § 103(a) over Sukenikk, in view of Vosika, et al. taken with Senter, et al. or Mueller, et al.

The rejection of claims 32-37 and 41-44 as allegedly being obvious over Sukenikk, et al. (WO 92/00047) in view of Vosika, et al. (WO 90/09798) taken with Senter, et al. (U.S. Pat. No. 5,306,307) or Mueller, et al. (U.S. Pat. No. 5,837,235), is respectfully traversed.

To establish a prima facie case of obviousness, three criteria must be met; (1) there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; (2) there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and (3) the publications must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142.

Rebuttal to the obviousness rejection of claims 32, 33, 41 and 42

Claims 32, 33, 41 and 42 are generally directed to a method of producing an implant which has an anchor molecule covalently bound to the surface of a metal, metallic alloy or ceramic implant material. The anchor molecule is then covalently bound to a mediator molecule that reduces rejection of the implant and/or promotes growing-in of the implant.

Sukenikk describes implant materials modified to selectively grow particular types of cells that come into contact with the implant. The implant is modified by attaching fibronectin to the implant surface. Sukenikk describes that fibronectin is linked by hydrogen bonding, van der Waals interactions or ion pairing between amino acid side chains of fibronectin and the distal functional groups of the molecules coupled to the substrate surface (page 22, lines 26-31). It is well known in the art that hydrogen bonding, van der Waals interactions and ion pairing are non-covalent forms of association. Since fibronectin is only non-covalently bound to the molecular monolayer, there will be a constant loss of fibronectin from the surface (so-called leaching) making this surface very unstable and unsuitable in particular as a long-term implant.

In contrast, the mediator molecules of claims 32, 33, 41 and 42 are covalently coupled to the anchor or spacer molecules, which, in turn, are covalently coupled to the implant surface. Therefore, the implant surface of Sukenikk et al., which contains non-covalently associated

fibronectin is not comparable to the instantly claimed implants which contain covalently linked mediator molecules such as BMP.

Vosika et al. describes the modification of an organic solid support material with a molecular monolayer in order to covalently attach cytokines. The solid support material with attached cytokines is used primarily to induce T-cell growth and/or activity. Vosika et al. fails to teach attachment of cytokines to implants which are metals, metallic alloys, or ceramic materials as required by the claims. In addition, the chemistry for covalently linking the cytokines to support materials disclosed by Vosika et al. only functions with organic materials e.g., polystyrene. The chemistry described in Vosika et al. is not suitable to facilitate coupling of the cytokines to inorganic materials or metals in significant amounts. Particularly, Vosika et al. does not address the difficulties connected to coupling biomolecules to inorganic surfaces, such as metal or ceramics, requiring, for example, the activation of a metal surface and the use of silane derivatives as anchor molecules.

Though Vosika et al. disclose in Example 1 the immobilization of an interleukin using glutaraldehyde to a support material, the disclosure points in a different direction from the present invention. Vosika et al., teaches, in particular at pages 21 to 24, that support materials, which are utilized in the *in vivo* process according to Vosika et al., are preferably biologically compatible and biodegradable. Suitable particulate supports fulfilling the requirements of the *in vivo* use proposed by Vosika et al. include the various organic biodegradable supports exemplified in the paragraph bridging pages 22 and 23. Vosika et al., also teaches to use polymer beads for attaching a cytokine to stimulate the growth of the cells. There is no hint in Vosika et al. which substrates besides fibers, microspheres, beads, particles, membranes, sheets and the like as stated in lines 31 to 33 on page 6 may be used. The cytokines are bound via the cytokine linking groups to the biodegradable supports, thus enabling the sustained release of the cytokines to the surrounding tissue.

Senter et al. describes microporous implants that may be impregnated with therapeutic agents prior to implantation and the implant may then function as a delivery vehicle for the impregnated therapeutic agents. Consequently, the therapeutic agents are not bound to the

surface of Senter's implants. Thus, Senter et al. is unable to cure the deficiencies of Sukenikk et al. and/or Vosika et al. noted above.

Mueller et al. also describes microporous implants as in Senter et al. Mueller's teachings are directed to preparing solid implanting materials on the basis of tissue particles which are suspended in a liquid to form a suspension, which is then deposited on a solid carrier. As in Sukenikk, an adhesion agent many be applied to the carrier or a growth factor may be deposited thereon. Mueller is also unable to cure the deficiencies of Sukenikk et al. and/or Vosika et al. because Mueller is entirely silent with respect to any covalent binding of BMP to any surface. As seen from lines 32-49 in column 3, the carrier material can be provided with growth factors, such as BMP, and wherein the carrier can be pulverulent and can give a pasty implant material or can be pre-shaped. Mueller further emphasizes (see, e.g., lines 50-55 in column 3) that the implant materials are suitable carriers in the form of a sponge, in the form of fibrils, or in the form of textiles which is inconsistent with the presently claimed subject matter where mediator molecules such as BMP are covalently bound to the implant.

Consequently, as no hint can be taken from Vosika et al. to covalently link mediator molecules to inorganic surfaces and as Sukenikk refers to non-covalent bonding by interaction of the surface with fibronectin (the only exemplified adhesion molecule), it cannot be considered obvious to transfer the teaching of Vosika et al. to Sukenikk et al. or vice versa.

Taking into account the teachings of Senter or Mueller, the skilled person would only understand that bone growth factors may promote the grow-in of a sponge-like implant soaked with a solution containing these bone growth factors. The skilled person would have had no incentive to covalently couple such bone growth factors to the surface of an implant. In contrast, considering the teaching of Sukenikk et al. the skilled person would have instead relied on the non-covalent attachment to the implant surface.

Thus, because the cited references alone or in combination fail to provide a prima facie case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rebuttal to the obviousness rejection of claims 35, 36, 43 and 44

Claims 35, 36, 43 and 44 are generally directed to a method of producing an implant that has an anchor molecule covalently bound to the surface of the implant material. The anchor molecule is then covalently bound to a BMP, ubiquitin or antibiotic mediator molecule that reduces rejection of the implant and/or promotes growing-in of the implant.

The deficiencies of the Sukenikk et al. with respect to covalent attachment of mediator molecules has been discussed above. Sukenikk et al. also fails to describe linkage to a mediator molecule which is BMP, ubiquitin or an antibiotic. Fibronectin is the only biomolecule which is attached to an implant by Sukenikk. Fibronectin, however, is used to mechanically fix cells to a surface and not alter the actual cell type or its basic functionality. This contrasts to a primarily functional molecule as used in the present invention, such as a morphogen, e.g. BMP-2. Thus, in the presence of BMP-2, a bone progenitor cell does not remain a progenitor cell but differentiates into an osteoblast which, in turn, differentiates into an osteocyte, which produces bone. A BMP coated surface is a "morphogenetic" surface inducing 3-dimensional bone growth, which is something entirely different from an adhesion-mediating surface as described Sukenikk et al.

Vosika et al. is unable to cure the deficiencies of Sukenikk et al. because Vosika et al. fails to disclose the use of a BMP protein, a ubiquitin, or an antibiotic for coating an implant surface. Moreover, Vosika et al. points to the treatment of malignant diseases, wounds and osteoporosis only and is not relevant to stimulation of bone implants (such as with BMP as a mediator molecule) designed for the replacement of functions such as hip and knee implants which stay in the body for 20-30 years. Consequently, no hint can be taken from Sukenikk et al. and Vosika et al. to covalently link the mediator molecules of the instant claims. Because Sukenikk refers to non-covalent bonding by interaction of the surface with the only exemplified molecule fibronectin, it cannot motivate combination of the teaching of Vosika et al. to that of Sukenikk et al. or vice versa.

As discussed in detail above, Senter et al. and Mueller do not teach or suggest covalent binding of BMPs, ubiquitin or antibiotics to an anchor molecule. Taking into account the teaching of Senter et al. or Mueller, the skilled person would only understand that bone growth factors may promote the grow-in of a sponge-like implant soaked with a solution containing these bone growth factors. However, the skilled person would have had no incentive to covalently couple such bone growth factors to the surface of an implant. In contrast, considering the teaching of Sukenikk et al. the skilled person would have instead relied on the non-covalent attachment to the implant surface as exemplified in Senter et al. and Mueller.

Thus, the cited references alone or in combination fail to provide a prima facie case of obviousness. Therefore, reconsideration and withdrawal of the rejection is earnestly solicited.

Rejection under 35 U.S.C. § 103(a) over Sukenikk, in view of Vosika, et al. taken with Senter, et al. or Mueller, et al. and further in view of Matsumoto, et al.

The rejection of claims 19, 23-25, 28 and 32-34 as allegedly being obvious over Sukenikk, et al. (WO 92/00047) in view of Vosika, et al. (WO 90/09798) taken with Senter, et al. (U.S. Pat. No. 5,306,307) or Mueller, et al. (U.S. Pat. No. 5,837,235) and further in view of Matsumoto, et al. (U.S. Pat. No. 4,371,612) is respectfully traversed. It is noted that claims 19, 23-25 and 28 have previously been cancelled. Thus, the rejection will be addressed with respect to claims 32-34.

As discussed in detail above, the combination of Sukenikk and Vosika taken in view of Senter or Mueller fails to provide a prima facie case of obviousness. The combination of art does not teach or suggest how a mediator molecule may be covalently coupled to an activated implant surface via a spacer molecule which is in turn coupled to an anchor molecule which is in turn coupled to the activated surface.

Matsumoto et al. describes the immobilization of biological material, such as enzymes, on microporous, water insoluble acrylonitrile polymers via covalent bonding, with the amino groups of the support material being either directly or via spacer molecules linked to the biologically active protein (column 5, lines 39-65). Matsumoto et al. does not suggest to use its

modified polymers as an implant much less suggest the particular implant materials of the present invention, nor the use of morphogens, such as BMP, to coat the implant surface. Thus, because the cited references alone or in combination fail to provide a prima facie case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

The rejections of claims 32-37 and 41-44 under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of United States Patent No. 6,635,269; and claims 38 and 39 in view of Matsumoto et al., is acknowledged. These issues will be addressed in due course pending resolution of all other issues in the case, e.g., by submission of a terminal disclaimer or other action as may be appropriate.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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